

## PAUL EHRLICH—AS MAN AND SCIENTIST\*

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PAUL EHRLICH is best known for his discovery of salvarsan (606) and as the father of chemotherapy. What is less known is the fact that he was a brilliant chemist, that he has made important contributions to our knowledge of bacteriology through his work on the staining of bacteria, and that he was one of the discoverers of the theory of immunology which has had such a profound influence on serotherapy and the use of antitoxins.

I never had the privilege of knowing Ehrlich personally, especially since he died in 1915, the year that I graduated from college. However, one of the first problems that engaged my attention after the completion of my doctorate work, dealt with the toxicity and effectiveness of salvarsan. Our entrance into the First World War and the great need for this drug which resulted from it led to the rapid development of its large scale production in this country. I became associated with one of the companies manufacturing it. It was my job to study its toxicity and other pharmacological properties in order to control its safe use. I became intensely interested in Ehrlich's work and became fascinated by his personality and by his method of scientific investigation.

Ehrlich was the first to lay emphasis upon the fact that the infecting agent may be more sensitive to treatment with chemical substances than the infected body cells. These ideas were quite contrary to the prevailing conception, as expressed by von Behring and by many others, that the host is usually poisoned more rapidly than the infecting germs by the action of chemical agents. Ehrlich's ideas pointed a way to sound and fundamental principles in the field of chemotherapy, which reached their particular heights with the discoveries of the sulfa drugs and antibiotics. Although it took a quarter of a century or more for these, rather than five or ten years as predicted by Ehrlich, they followed the path laid down by him.

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Paul Ehrlich was born in a small town in Silesia in 1854. His mother appeared to influence greatly his early education. In school, he was a brilliant scholar, some of his friends referring to him as a "Lernkopf." His extreme modesty prevented him, however, from asserting himself. He was particularly interested in ancient languages, in mathematics and in natural sciences. He was apparently not too fond of schoolwork, since he was always looking forward to his return to his "laboratory," a room in his parents' house, which he fixed up for chemical studies with dyes and for his biological collections.

At an early age, Ehrlich learned to combine theory with praxis. Thus his observations on the adsorption of methylene blue upon the nervous tissues led him to postulate the potential practical utilization of this reaction for disease control. The story is told that when he had to write an essay on "Life as a Dream," he described life as dependent upon normal oxidation processes, nerve activity being one such process; a dream is a form of oxidation, resulting in the phosphorescence of the brain. This scientific exposition by a mere youth of an idea where a poetic outburst was no doubt expected hardly satisfied his examiner.

Ehrlich became interested at an early age in the problem of staining tissues and cells. His cousin, Karl Weigert, somewhat older than he, who had already made an outstanding contribution to the staining of bacteria, served as a model for his future scientific development and aroused especially his interest in dyes.

As is usually customary for German students, Ehrlich studied medicine at several universities, namely in Breslau, Strassburg, and Leipzig. He received his M.D. from the latter in 1878. At Strassburg, Ehrlich came under the influence of the anatomist Waldeyer and at Breslau, under that of the pathologist Cohnheim, both of whom greatly admired his zeal and scientific interests. In his early experiments, he discovered a new variety of cells, "mast-cells." His Doctor's thesis dealt with the subject of "Chemical and histological staining principles using aniline dyes." The youthful scientist developed the idea of chemical reactions of heterogeneous substances with the cell protoplasm, which was later to lead to his famous side-chain theory. His experience in staining was made good use of in his first position as assistant in Charité Hospital in Berlin. The urine and blood preparations which Ehrlich made were soon to become famous. These were so well made that he could follow the course of disease, especially in the case of typhoid patients.

While listening to Robert Koch's famous announcement, made in

1882, of the discovery of the tubercle bacillus, Ehrlich remembered the rods which he usually saw in the sputum of tuberculosis patients. He joined Koch in the further elucidation of the problem of the etiology of this disease. This was the beginning of Ehrlich's interest in bacteriology.

Ehrlich was often spoken of as a "born chemist." Only by combining a medical training, an appreciation of biological reactions with chemical perspicacity, was he able to obtain a profound insight into the problems of disease, of body immunity and of chemotherapy, which laid the foundation for the new science of the nature and control of infectious diseases.

His early interests in staining techniques led him to a study of the distribution of dyestuffs in the animal body. As a result of these studies, he was able to differentiate and classify various types of body cells, particularly the blood leukocytes. This was followed by studies of vital staining, whereby the various dyes were found to be specific in their staining capacity of different organs or cells. As a result of these and other studies, Ehrlich concluded that "the ways and means by which drugs are distributed through the body must be of the greatest importance in the rational development of therapeutics."

In 1887, Ehrlich himself contracted tuberculosis. This forced him to leave for Egypt where he spent the next two years. Upon his return he continued his collaboration with Koch. He also helped von Behring in his work on diphtheria antitoxin. Unfortunately, the last collaboration ended disastrously, because of the personality of von Behring, who did not give Ehrlich sufficient credit for his important contribution, which alone made possible the large-scale production and practical utilization of antitoxins. He also introduced standards for measuring the potency of antitoxins and defined the units of their activity.

Ehrlich not only established the principles fundamental to the measurement of activity of biological agents, but he also elucidated the nature of the reaction whereby the body becomes immune to further infection. The formation of antibodies, or substances which tend to neutralize the infective agent or poison, was thereby recognized as the important mechanism with which the body tends to combat disease. Immunology and allergy are greatly indebted to Ehrlich's fundamental work.

Thus began, on the part of Ehrlich, a search for substances which would combine and destroy, neutralize, or weaken the infecting organism without injuring the patient. He first tested, in 1891, the possi-

bilities of methylene blue in the treatment of malaria. In 1902, with experimental animals at his disposal, he began to develop the field of "chemotherapy," which led to the discovery of chemical substances which would have a harmful effect upon the infecting parasite without injuring the host. Ehrlich made a sharp differentiation between the "parasitotropic" and the "organotropic" effect of antimicrobial agents. He recognized the fact that serum therapy is not effective in all infectious diseases, notably those caused by protozoa and protozoan-like organisms. His future discoveries were, therefore, directed largely upon the latter.

Ehrlich was appointed as Director of the State Institute for the Control of Sera at Steglitz and later at Frankfurt. He was soon made Director of the Serum Institute, where he made his classical contributions to immunotherapy and where he developed his ideas on the "side-chain" theory of immunity. Finally, he became Director of the Georg Speyer-House, where he was to spend the rest of his life.

In 1884, Ehrlich was made a titular professor, without being proposed, however, to a University Chair for fifteen years. Between 1877 and 1914, he published 232 scientific papers and books. In addition there were published more than 400 papers by his assistants and collaborators.

His first experiments in chemotherapy were made in 1891. This was a result of his work with dyes and vital staining. The discovery that methylene blue stained the malarial parasite led him to try the effect of this dye on malarial patients. Some patients benefited by such treatment. Although the results were not conclusive, they led later to the discovery by others of the important antimalarial drugs atebirin and plasmoquin.

Ehrlich's important contribution to immunology was published in 1897. His work on the fixation of oxygen by certain groupings in the protoplasm led him to the idea of the presence in the protoplasm of numerous other "receptors," whereby various foodstuffs are anchored prior to their incorporation in the cell. The toxins and antigens also combined with specific receptors of the cell; the latter was thus forced to replace the receptors by new ones in excess; these finally broke off and found their way into the blood, thus serving as specific antitoxins or antibodies.

These studies led Ehrlich to a thorough investigation of trypanosome infections. These resulted in the examination of the benzopurpurin series of drugs, which led him to trypan red and other compounds, and finally

to the arsenical drugs. He laid particular emphasis on the chemical combinations of the drugs with the parasite, as against their effect upon the tissues of the host.

The concept of chemotherapy developed by Ehrlich, as mentioned above, was made possible only through the property of certain chemical substances to act selectively upon different living cells. Ehrlich's preliminary work on the effectiveness of atoxyl as a chemotherapeutic agent led directly to his discovery of salvarsan, the "magic bullet." This was the first true chemotherapeutic agent that came out of a chemical or biological laboratory. It opened a new field in the treatment of human diseases. In introducing this drug into practical therapy, Ehrlich laid great emphasis upon the curative dose vs. the tolerated dose. He finally came to recognize the importance of the "therapia sterilisans magna," or the single shot treatment of infections.

The careless use of salvarsan by many doctors resulted in a number of serious reactions which were often blamed on Ehrlich and upon his discovery. I well recall how one day in 1918 a practicing doctor from a small town in North Jersey came to see me to inquire whether I would be willing to instruct him in the manner of treating syphilitic patients with this drug. On arriving at the agreed time, at the Doctor's office, I found in the chair a bulky fellow, a chauffeur by profession, who had just returned from Europe where he had contracted the disease. I brought with me a sample of the salvarsan manufactured by the company with which I was associated and demonstrated to the doctor and to several of his colleagues, assembled for this occasion, how to prepare the solution of the drug, how to neutralize it, how to find the vein in the arm of the patient. Following my instructions, the doctor made the injection. The patient got up, feeling quite well, and left the office, after being told to return in a week for a second injection. A few months later, I walked again through one of the main streets of that town. I was suddenly accosted by a thin emaciated man, a mere shadow of the patient whom I saw in the chair a few months earlier. He exclaimed: "You are the one man for whom I have been looking these past few months." He then proceeded to tell me that after he was given the second injection, he had to be carried out of the office on a stretcher. Upon leaving the hospital two or three months later, he had decided to determine just what happened to him. He was, therefore, on the constant lookout for me, since he knew that I was the only one who could tell him what was wrong with the manner in which he was given the second treatment. It

took me some time to establish the fact that the doctor had added to the salvarsan a great excess of a highly concentrated solution of sodium hydroxide, which was then injected into the patient's vein. I could, of course, hardly be a witness to the negligence of the doctor.

Ehrlich had to pay dearly, both in time and energy, in order to have the medical profession follow the detailed instructions concerning the use of salvarsan (No. 606). He fully recognized the need for observing in minutest detail the various precautions required in the use of this drug. He emphasized particularly the danger in using contaminated water. When news reached him of cases of deafness and neural relapses resulting from the use of salvarsan, he was much upset. He took it upon himself to instruct the doctors in its proper use. When he discovered neosalvarsan (No. 914), some of the difficulties experienced in the use of salvarsan tended to be overcome.

We have heard recently much discussion of the importance of "chance" vs. "systematic investigations" in scientific discoveries. Ehrlich's work had left little to chance. He was a great believer in teamwork, which has played such an important part in the recent discoveries of antibiotics. He expresses this as follows: "Centralization of investigation with independence of the individual worker." He was a great believer in the careful planning of research. However, the individual experiments were constantly modified as work progressed. He did not appear to attach much importance to the differentiation between "pure" and "applied research."

Unexpected observations were made great use of in the solution of given problems. It so happened that the kitchen maid forgot to remove the slides with his stained preparations of the tuberculosis organism from the stove. This led Ehrlich to recognize the importance of heating slides in making certain stains. But it was his systematic, unfailing, driving power, and faith in finding in time the right answer that produced his greatest discoveries. When one of his assistants tested in 1908 the effect of 606 in experimental syphilis and reported negative results, Ehrlich was convinced that something was wrong. Next year, in 1909, when the Japanese investigator Hata came to his laboratory, he was instructed to test this preparation very carefully. Positive results were now obtained thus confirming fully Ehrlich's expectations.

Paul Ehrlich represented the true scientist who does not sit idly by in deep contemplation waiting until a chance will come his way, but who searches information in every branch of science that can only

elucidate his particular problem. In his case, he devoted time and energy to cell respiration, to the action of dyes, to problems of immunity, to the nature of malignant growths, and to the selective action of chemical agents.

Following the discovery of salvarsan, honors began to pour in on Ehrlich including the Nobel prize which he shared with Metchnikov. When his 60th anniversary was celebrated in 1914, there came to him congratulations from all over the world and numerous distinctions from his own and other governments. The expression of gratitude of patients cured by salvarsan only partly tended to balance the abuse heaped upon him by some of the physicians who were hostile to its use. The outbreak of the First World War came as a final shock to him which finally led him to his early grave.

Ehrlich was a modest man. He was an optimist. He struggled his whole life for the advance of human health and the eradication of disease. He had a hasty temperament, but he was also very kind. It was said of him that "he could be loved as a child." The British bacteriologist Bulloch spoke of him as the "most extraordinary man I ever met; with his wonderful inspiration, his enormous power of work, his astonishing knowledge, he was the greatest man in the medical world of his time. He was modest, sincere, noble-minded, and with the greatest kindness and consideration towards everybody."

His own countryman, another great scientist whose life and work had in some respects a certain similarity to that of Ehrlich, Richard Willstätter wrote down his impressions of Ehrlich, when he came to Frankfurt, on March 14, 1914, to participate in the celebration of Ehrlich's 60th birthday. I am translating rather freely: "Ehrlich was a simple, basically good man, whenever he only had time for it. He concentrated entirely upon his indefatigable work, which drove him constantly from one experiment to another. His creative phantasy was always at work preparing him for new working hypotheses. His great capacity combined imagination with experiment. His persistence assured its success. Without being a chemist by training, he had the most unique experience in establishing the reactions of dyes in the broadest possible sense. His working cabinet, as well as his laboratory, was small. Each table and each chair was covered with books, reprints, memoranda, flasks and tubes of every possible form, and cigar boxes. The latter contained either imported cigars or tubes containing various chemical preparations. He knew and could find everything that was

there, even if it took a long time to look for it. His knowledge in his selected field was extensive and profound, although also one-sided. He could hardly afford the time to accumulate knowledge which would not serve to advance his own selected field for science."

Miss Marquardt, his secretary, describes him as follows:

"Ehrlich's manner was friendly and jovial to all around him, his fellow-workers, assistants and employees. New-comers, or people whose work did not often bring them in contact with the Chief, were, however, often a little embarrassed and uneasy when they had to see him, in spite of his amiability. This was partly because Ehrlich's exuberant manner made it hard to grasp his meaning at first, and his directions were always given with suggestions and allusions only. Also there was a little imp in him which made him make joking remarks with an absolutely serious face, and this, with his habit of making fun of himself, confused some people who were not used to it. Those who knew him well, however, could always guess what he wanted from the slightest hint.

"Ehrlich judged his fellow-workers and employees entirely by their knowledge and ability and the work actually done, and often thought it right to ignore weak points of character. He said that the private life of those who worked with him did not concern him providing they did their duty well, and he never listened to gossip or scandal."

Ehrlich neglected his health completely. All who knew him commented on his endless work, continuous smoking, and his irregularity of eating. He was indifferent to the comforts of life. He was generous to his assistants. He was very careful to give them full credit for their work. Among his most outstanding collaborators, one need only mention Morgenroth, Neiszer, Sachs, Shiga and Hata.

Need I emphasize again the fact that Ehrlich's work had a profound influence upon the development of microbiology as a whole and upon chemotherapy in particular. Humanity is greatly indebted to Ehrlich. Together with Louis Pasteur, Robert Koch and Elie Metchnikov, Paul Ehrlich has laid the foundation for modern therapeutic war on human and animal diseases. At a time when so much energy is being spent for the machines of destruction, the contributions of Paul Ehrlich and others who have followed in his footsteps have served the purpose of the saving of human life and of making this world a better and healthier place to live in.